Observations on Cardiac Output, Peripheral Blood Flow and Blood Volume in Hypertension— Before and During Treatment

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There is general agreement among investigators that the total blood volume and cardiac output are normal in uncomplicated hypertension. The cardiac output is maintained in the normal range, however, by an increase in the residual volume of the left ventricle which comes about as follows: If aortic pressure is suddenly elevated from the normal to the hypertensive range the stroke volume of the left ventricle diminishes owing to the increased resistance to outflow. The retained blood increasing from beat to beat distends the ventricular chamber and stretches the myocardial fibers. Since, according to Starling's law, the force of contraction is proportional to the diastolic fiber length, the strength of ventricular contraction increases from beat to beat until a point is soon reached at which output is restored but at the expense of an increased residual volume in the left ventricle. Also, since the heart now is performing more work than it had previously, hypertrophy of the muscle fibers gradually occurs.

This process of compensation has its limitations beyond which further increases in diastolic fiber length result in progressively diminishing rather than increasing cardiac output. The point at which failure occurs varies from heart to heart depending on other factors such as patency of the coronary circulation, other disease states affecting the myocardium, metabolic abnormalities, and so on.

When the heart fails in hypertension the symptoms often are those of pure left ventricular failure, but decompensation may begin with signs of right ventricular failure. The reasons for this appear to be various. First, the myocardium is a syncytium involving both ventricles. When the contraction of the stronger, or left, ventricle is weakened it compromises to some extent the contraction of the right. Second, failure of cardiac output and reduction of aortic and carotid sinus pressures stimulate reflex sympathetic vasoconstriction, including venoconstriction, which shunts blood into the central veins and right heart. Third, reduction in the velocity and momentum of the blood tends to displace a greater proportion of the blood volume to the venous side. Fourth, the fall in cardiac output through unknown pathways stimulates aldosterone secretion and renal conservation of salt and water. This leads to an increase in total extracellular (including plasma) volume and further aggravates venous congestion.

Peripheral blood flow appears to be normal in hypertension and the pe-

ripheral resistance seems to be more or less uniformly increased throughout the body. Renal blood flow, however, often is decreased moderately.

EFFECTS OF GANGLIONIC BLOCKING AGENTS

When a ganglionic blocking agent such as hexamethonium is injected intravenously into a patient with essential hypertension not complicated by congestive heart failure there is a decrease in mean arterial pressure and cardiac output without change in the total peripheral resistance. Central venous and right heart pressures fall, indicating a reduction in venous return.[1] This reaction can be studied in more detail in the dog by substituting a constant output pump for the left ventricle, leaving the right ventricle undisturbed.[2] Blood is drained from the left auricle into a reservoir from which it is pumped into the aorta through a T tube. The right ventricle is not by-passed in this preparation, only the left ventricle being substituted for by the pump.

When hexamethonium is injected into such a preparation there is at first a decrease in systemic arterial pressure indicating arteriolar relaxation, since the left pump output is maintained at a constant rate. Within one minute, this is followed by a reduction in right ventricular output and pulmonary arterial pressure. During the succeeding few minutes the reservoir level falls as several hundred ml. of blood are transferred from the reservoir to the animal's vascular system. Obviously, the vascular volume or capacity of the dog had *increased* following hexamethonium and to an extent that could be explained only by assuming capillary and venular as well as arteriolar dilatation. As a corollary to this, it can be shown that sympathetic stimulation as exemplified by norepinephrine produces exactly opposite effects, indicating a decrease in peripheral vascular volume. Many other investigators have brought forth evidence to show the relationship between the sympathetic nervous system and the peripheral vascular system including venous tone, right heart filling pressure and cardiac output.[3-6]

In hypertensive patients with congestive heart failure the cardiac output increases after the administration of hexamethonium rather than decreases, and the total peripheral resistance declines.[1] Pulmonary, right heart and central venous pressures also fall toward normal. Dual effects operate in this case to produce the improvement. First the decrease in aortic pressure reduces the work demand and permits greater left ventricular emptying. The overstretched left ventricular diastolic fiber length is reduced to a point where the myocardium can contract more effectively. Second, the increase in peripheral vascular capacity drains blood away from the congested central veins, permitting reduction in the overdistention of the right ventricle.

Release of sympathetic tone using ganglion blocking drugs does not result in an even distribution of blood flow to the various regions of the body. Foot and hand blood flow increase many fold, particularly if their vasculature is under increased tone as occurs during exposure to cold environmental temperatures. Muscle blood flow increases, whereas splanchnic (hepatic-portal) blood flow declines. Renal blood flow decreases temporarily, but in the absence of severe renal damage the blood flow soon is restored owing to the marked autonomy of the renal vasculature. These data do not indicate that the sympathetic nervous system is of great importance in regulating arteriolar tone in the resting, supine subject except for its role

in temperature regulation of the skin of the distal extremities. The results also emphasize the fallacies inherent in drawing conclusions as to the overall vasodilating effects of agents which increase skin temperature, color or blood flow.

The sympathetic nervous system is undoubtedly of great importance in adjusting cardiac output, arterial pressure and central venous pressure. When the cardiac output and arterial pressure fall, owing to blood loss or blood volume shifts such as occur on assuming the erect position, the baroreceptor reflexes initiate sympathetic reflex vasoconstriction. This not only initiates arteriolar constriction but also reduces peripheral vascular capacity and shunts blood into the central circulation. Following sympathetic inhibition with hexamethonium the arterial pressure becomes a direct function of the blood volume.[7] If the blood volume is reduced by venesection in the supine, hexamethonium-treated subject, a perceptible step-wise fall of arterial pressure occurs with each 50 cc. removed, and as this is reinfused the pressure rises step-wise back to the prephlebotomy level.

SALURETIC AGENTS

The effect of saluretic agents or salt-depleting diets on the cardiac output and arterial pressure is similar in some ways to the action of the ganglionic blocking agents. However, the effect is produced through an entirely different mechanism which will be considered in more detail in the section on pharmacology. In this section it is sufficient to make the following comparisons: both the ganglion blocking drugs and the saluretic agents appear to lower blood pressure by reducing right heart filling pressure and cardiac output. Ganglionic blockers accomplish this by increasing peripheral vascular volume in relation to an unchanged total blood volume. Saluretic agents and salt-depleting diets function by reducing total blood, specifically plasma volume, in the presence of an apparently unchanged or insufficiently reduced vascular volume or capacity. Reduction in tissue pressure also may be a contributing factor.

HYDRALAZINE

The effects of hydralazine or Apresoline on cardiovascular hemodynamics are entirely different from those already described. This drug produces changes which mimic those seen in fever. It should be recalled that the hemodynamic effects of pyrogens still occur even after the febrile response is blocked with antipyretics.[7]

After hydralazine the cardiac output approximately doubles. Since mean arterial pressure falls, the total peripheral vascular resistance declines more profoundly than is the case with any other antihypertensive drug. Because of this the decrease in diastolic pressure is prominent. Because of the increased stroke volume, however, systolic pressure is less affected.

Hydralazine produces a characteristic redistribution of blood flows to various areas. Blood flow is diverted primarily to the hepatic-portal and renal areas which exhibit significant increases.[8, 9] Teleologically this would be of obvious importance to an organism attempting to combat a pyrogenic infection. Blood flow through the muscles of the extremities usually decreases slightly while digital or skin blood flow shows no significant change.[9] Coronary blood flow increases.[10]

THE VERATRUM ALKALOIDS

Following Veratrum viride the cardiac output does not change significantly unless the patient has congestive heart failure, in which event it increases.[11] When the pulmonary arterial pressure is normal it does not change, but when it is elevated as in congestive heart failure it falls toward normal as the cardiac output increases. Total peripheral resistance is reduced in all cases.

The bradycardia, but not the hypotension, is vagal in origin and can be blocked with atropine. Homeostatic, vasoconstrictor reflexes ordinarily are not blocked by Veratrum. Blood flow through muscular, renal and hepatic-portal areas shows no essential change although there may be initial decreases.

As can be seen from these studies, clinical effectiveness is not necessarily associated with complete reversal of the hypertensive process. Thus, of all the antihypertensive agents studied, Veratrum produces the most physiologic, hemodynamic reversal of hypertension. On the other hand, more effective drugs clinically, such as chlorothiazide and the ganglion blocking drugs, decrease cardiac output and produce other hemodynamic abnormalities. It would appear that rather marked hemodynamic aberrations can be tolerated with benefit to the patient provided they reduce his blood pressure.

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